Complete Summary

GUIDELINE TITLE

K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients.

BIBLIOGRAPHIC SOURCE(S)

National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 2005 Apr;45(3 Pt 2):16-153. [736 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s)/intervention(s) for which important revised regulatory and/or warning information has been released.

- August 16, 2007, Coumadin (Warfarin): Updates to the labeling for Coumadin to include pharmacogenomics information to explain that people's genetic makeup may influence how they respond to the drug.
- June 8, 2007, Troponin-I Immunoassay: Class I Recall of all lots of the Architect Stat Troponin-I Immunoassay. The assay may report falsely elevated or falsely decreased results at and near a low level, which may impact patient treatment.
- October 6, 2006, Coumadin (warfarin sodium): Revisions to the labeling for Coumadin to include a new patient Medication Guide as well as a reorganization and highlighting of the current safety information to better inform providers and patients.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Cardiovascular disease (CVD) including:
  - Coronary artery disease (CAD)
  - Cardiomyopathy
  - Valvular heart disease (VHD)
  - Arrhythmia
  - Cerebrovascular disease (CBVD)
  - Peripheral vascular disease (PVD)
- Chronic kidney disease (CKD) requiring dialysis

GUIDELINE CATEGORY

Evaluation
Management
Risk Assessment
Screening
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Internal Medicine
Nephrology
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Physicians

GUIDELINE OBJECTIVE(S)

- To facilitate the evaluation, identification, and treatment of patients on dialysis with cardiovascular disease (CVD), recognizing that all patients on dialysis are at increased risk for cardiovascular disease
- To highlight those aspects of cardiovascular care that are different or have been construed to be different in dialysis patients compared to the general population, either as a consequence of the kidney disease or the dialysis procedure

TARGET POPULATION

Adult and pediatric patients with chronic kidney disease Stage 5 requiring renal replacement therapy/dialysis with or at risk for cardiovascular disease

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

Initial and on-going assessment for cardiovascular diseases and screening for traditional and nontraditional risk factors

1. Assessment of signs and symptoms, including assessment of arterial pulse and skin integrity in peripheral vascular disease (PVD)
2. Echocardiography, including exercise or pharmacological stress echocardiogram
3. Electrocardiography
4. Nuclear imaging tests
5. Assessment for hemorrhagic risk and presence of anemia
6. Duplex testing for PVD
7. Blood pressure evaluation
8. Measurement of physical functioning
    - Performance testing or questionnaire
    - Assessment of potential barriers to performance in physical activity
9. Assessment of psychological state with focus on depression, anxiety, or hostility
10. Determination of pulse pressure
11. Radiography
12. Intact parathyroid hormone assay
13. Special considerations in dialysis patients
    - Coronary artery disease (CAD): Use of iso-osmolar radiocontrast media (iodixanol) with or without *N*-acetylcysteine in angiographic studies
    - Valvular heart disease (VHD): optimization of dry weight prior to testing and consideration of relationship between echo exam and hemodialysis treatment or presence/absence of peritoneal dialysis fluid when interpreting evaluations.

Management/Treatment

Cardiovascular Diseases

Acute Coronary Syndromes (ACS)

1. Standard therapy (percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG], antiplatelet agents, beta-blockers, thrombolytic therapy, lipid-lowering agents) with attention to drugs that have altered clearance in kidney failure (e.g., low molecular weight heparin)
2. Acute reperfusion therapy for dialysis patient with ST-segment elevation myocardial infarction (MI)

Chronic CAD

1. Standard pharmacotherapy (acetylsalicylic acid [ASA], beta-blockers, nitroglycerin, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], statins, calcium channel blockers [CCB])
2. Unique aspects include maintenance of hemodynamic dry weight and hemoglobin levels, modification of dosing regimens, and use of loop diuretics
3. Surgical interventions, including CABG and PCI with conventional or drug-eluting stent

VHD

1. Standard management, including mechanical or tissue valve replacement

Cardiomyopathy

1. Standard therapy with attention to potential effects of therapeutic agents (e.g., ACE inhibitors, beta-blockers) on intrahemodialytic hemodynamics
2. Empirically individualized dosing
3. Maintenance of euvolemia and adjustment of targeted dry weight

Dysrhythmia

1. Standard therapy, including antiarrhythmic agents (including beta-blockers) with dosing adjustments and pacing devices, including internal defibrillators

Cerebrovascular Disease

1. American Heart Association guidelines with careful monitoring of anticoagulation and imaging to localize thrombotic or bleeding events
2. Standard medical and surgical management of transient ischemic attack (TIA) and stroke with assessment of risk of bleeding with use of thrombolytics in hemodialysis patients

PVD

1. Standard therapy (smoking cessation, lipid-lowering therapy, glycemic control, blood pressure control, ACE inhibitors, antiplatelet agents)
2. Supervised exercise regimens
3. Medication to increase vasodilation

Cardiovascular Risk Factors

Diabetes

1. Treatment according to American Diabetes Association guidelines

Blood Pressure

1. Management of fluid status through education and counseling, low sodium intake, increased ultrafiltration, longer and/or more frequent dialysis, and drugs that reduce salt appetite

2. Adjustment of antihypertensive drugs, including use of ACE inhibitors or angiotensin II-receptor blockers and timing of treatment

Dyslipidemia

1. Previous Kidney Disease Outcomes Quality Initiative (K/DOQI) Guidelines

Smoking, Physical Activity, and Psychological Factors

1. Counseling to stop smoking and increase activity level
2. Appropriate referral to specialists (e.g., smoking cessation, physical therapist)
3. Treatment for depression, anxiety, or hostility, as appropriate

Anemia

1. Previous K/DOQI Guidelines

Arterial Stiffness, Vascular and Valvular Calcification, Phosphorus and Parathyroid Hormone

1. Non-calcium-containing phosphate binder
2. Adherence to current guidelines for treatment of calcium, phosphate, and parathyroid hormone

General

1. Ensuring availability of external cardiac defibrillators in dialysis units

MAJOR OUTCOMES CONSIDERED

- Cardiovascular outcomes
- Morbidity
- Mortality
- Survival
- Myocardial infarction

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search

The Work Group and Evidence Review Team decided in advance that a systematic process would be followed to obtain information on topics that relied on primary articles. Only full journal articles of original data were included. Editorials, letters,

and abstracts were not included. Selected review articles were included for background material. Though reports of formal studies were preferred, case series were also included. No systematic process was followed to obtain textbooks and review articles.

Studies for the literature review were identified through MEDLINE searches of English language literature conducted between March and October 2002. These searches were supplemented by relevant articles known to the domain experts and reviewers through December 2003.

The MEDLINE literature searches were conducted to identify clinical studies published from 1966 through the search dates. The primary search was designed to capture studies pertaining to all topics. Supplemental searches were made to maximize retrieval of studies pertaining to specific topics, including: anxiety and hostility, carnitine, diet, hormone replacement therapy, pediatrics, and peripheral vascular disease. Development of the search strategies was an iterative process that included input from all members of the Work Group. The text words or MeSH headings for all topics included "renal replacement therapy," end-stage renal disease and related terms. The searches were limited to studies on humans and published in English, and focused on either adults or children, as relevant.

MEDLINE search results were screened by members of the Evidence Review Team. Potential papers for retrieval were identified from printed abstracts and titles, based on study population, relevance to topics, and study size. For studies of risk factors and treatments, those with fewer than 10 subjects were excluded; for epidemiology studies, those with fewer than 30 subjects were excluded. Studies of risk factors had to evaluate a cardiovascular outcome to be included. Studies of risk factor or cardiovascular treatments, including surgery, had to be comparative; thus single-cohort case series were excluded. After retrieval, each paper was read to verify relevance and appropriateness for review, based primarily on study design and ascertainment of necessary variables. Some articles were relevant for two or more topics. Domain experts made the final decision for inclusion or exclusion of articles. All articles included were extracted and are contained in the summary tables. Numerous additional articles that did not meet the specific criteria necessary to qualify for inclusion were reviewed, with or without extraction, for use as background material.

In an iterative process, the topics for which articles would be analyzed in depth and summarized were restricted to those topics that had not been sufficiently summarized previously by other Kidney Disease Outcomes Quality Initiative (K/DOQI) Work Groups or others and provided evidence for the specific guidelines. For most topics, given the small number of available studies, all comparative studies with at least 10 dialysis patients per arm were included. For certain topics with relatively large numbers of studies, stricter criteria were used. For studies of serum calcium, phosphorus, and parathyroid hormone (PTH) as predictors of cardiovascular disease (CVD), only studies that reported that they were sufficiently powered for these predictors were included. Studies that evaluated tobacco use as a risk factor for CVD had to both define smoking use categories *a priori* and have a minimum of 100 subjects. Studies of both lipoprotein(a) [Lp(a)] and genetic markers were required to have at least 10 subjects with CVD outcomes. For predictors with sufficient numbers of studies, only associations with CVD event outcomes were included. These included C-

reactive protein, random serum troponin levels, smoking, echocardiogram measurements, and surgical interventions for coronary artery disease. Intermediate outcomes, including vascular calcification, intima-media thickness, and ventricular arrhythmia were included for other predictors analyzed. For certain predictors, studies were also included that reported prevalent (as opposed to future) CVD. These included genetic markers and ankle-arm brachial index.

NUMBER OF SOURCE DOCUMENTS

Overall, 16,691 citations were screened (9,078 from the primary search; 7,613 from supplemental searches), from which 396 articles were retrieved and reviewed. An additional 151 articles, added by Work Group members and domain experts, were reviewed. Of these, a total of 86 articles met sufficient criteria to be included in summary tables.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Strong: Evidence includes results from well-designed, well-conducted study/studies in the target population that directly assess effects on health outcomes.

Moderately strong: Evidence is sufficient to determine effects on health outcomes in the target population, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; OR evidence is from a population other than the target population, but from well-designed, well-conducted studies; OR evidence is from studies with some problems in design and/or analysis; OR evidence is from well-designed, well-conducted studies on surrogate endpoints for efficacy and/or safety in the target population.

Weak: Evidence is insufficient to assess the effects on net health outcomes because it is from studies with some problems in design and/or analysis on surrogate endpoints for efficacy and/or safety in the target population; OR the evidence is only for surrogate measures in a population other than the target population; OR the evidence is from studies that are poorly designed and/or analyzed.

The strength of evidence for a group of studies was graded using a rating system that takes into account:

1. Methodological quality of the studies
2. Target population (patients on dialysis or other populations)
3. Study outcomes (health outcomes or surrogate measures for those outcomes)

(See table 42 in the original guideline document).

METHODS USED TO ANALYZE THE EVIDENCE

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Data extraction forms were designed to capture information on various aspects of the primary articles. Forms for all topics included study setting and demographics, eligibility criteria, causes of kidney disease, numbers of subjects, study design, study funding source, dialysis characteristics, comorbid conditions, descriptions of relevant risk factors and cardiovascular outcomes, statistical methods, results, study quality (based on criteria appropriate for each study design, see below), study applicability (see below), and sections for comments and assessment of biases.

Training of the Work Group members to extract data from primary articles occurred at meetings, and subsequently by e-mail and during teleconferences.

Format for Evidence Tables

Two types of evidence tables were prepared. Detailed tables contain data from each field of the components of the data extraction forms. These tables were used to efficiently track and transmit data about all extracted studies. They were completed by the Evidence Review Team from extraction forms filled out by Work Group members. They were then given to the Work Group members, but are not included in the report.

Summary tables describe the strength of evidence according to four dimensions: study size (of both hemodialysis [HD] and peritoneal dialysis [PD] patients) and duration, study applicability, results and methodological quality. Within each table, the studies are first grouped by outcome type. Outcomes are ordered by all-cause death, cardiovascular death, and cardiovascular events. Studies with intermediate and prevalent outcomes are shaded at the bottom of the tables. Within each outcome, studies are ordered first by methodological quality (best to worst), then by applicability (most to least) and then by study size (largest to smallest). When relevant, outcome thresholds (e.g., of troponin I levels) or definitions of predictors (for genetic predictors) are included. Results are presented using summary symbols, as defined in the original guideline document. An example of an evidence table is shown in table 39 of the original guideline document.

Study Size and Duration

The study (sample) size is used as a measure of the weight of the evidence. In general, large studies provide more precise estimates of prevalence and associations. In addition, large studies are more likely to be generalizable; however, large size alone does not guarantee applicability. A study that enrolled a large number of selected patients may be less generalizable than several smaller studies that included a broad spectrum of patient populations. Similarly, longer duration studies may be of better quality and more applicable, depending on other factors.

Applicability

Applicability (also known as generalizability or external validity) addresses the issue of whether the study population is sufficiently broad so that the results can be generalized to the population of interest at large. The study population is typically defined primarily by the inclusion and exclusion criteria. The target population was defined to include patients with end stage renal disease (primarily those on dialysis). A designation for applicability was assigned to each article, according to a three-level scale. In making this assessment, sociodemographic characteristics were considered, as were the stated causes of chronic kidney disease, and prior treatments. Applicability referred to either the hemodialysis population or the peritoneal dialysis population, as appropriate.

Results

In general, the result is summarized by both the direction and strength of the association. Depending on the study type, the results may refer either to dichotomous outcomes, such as the presence of a specific genotype or a laboratory test above or below a threshold value, or to the association of continuous variables with outcomes, such as serum laboratory tests. The magnitude of the association and both the clinical and statistical significance of the associations were considered. Criteria for indicating the presence of an association varied among predictors depending on their clinical significance. Both univariate and multivariate associations are presented.

For studies of troponin I and T, sensitivity and specificity data are included when reported. For clarity, the results for studies of surgical interventions for coronary artery disease are presented as **coronary artery bypass graft (CABG), Stent,** or **Tissue** to indicate studies for which the intervention had significantly better outcomes, or coronary artery bypass graft for studies where there was a trend toward better outcomes with coronary artery bypass graft.

Quality

Methodological quality (or internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of types of design were evaluated, a three-level classification of study quality was devised (see original guideline document).

Summarizing Reviews and Selected Original Articles

Work Group members had wide latitude in summarizing reviews and selected original articles for topics that were determined not to require a systemic review of the literature.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The overall aim of the project was to develop clinical practice guidelines for the evaluation and management of cardiovascular disease (CVD) in chronic kidney disease (CKD) patients who require either hemodialysis (HD) or peritoneal dialysis (PD).

The Work Group sought to develop the guidelines using an evidence-based approach. Evidence regarding the guideline topics was derived from a systematic summary of the available scientific literature on the epidemiology of cardiovascular disease among dialysis patients, the evaluation and management of cardiac, cerebrovascular, and peripheral vascular disease among dialysis patients, the evaluation and management of specific risk factors for cardiovascular disease among dialysis patients, and cardiovascular risk stratification among dialysis patients.

Refinement of Topics and Development of Materials

The Work Group and Evidence Review Team developed a) draft guideline statements; b) draft rationale statements that summarized the expected pertinent evidence; and c) data extraction forms requesting the data elements to be retrieved from the primary articles. The topic refinement process began prior to literature retrieval and continued through the process of reviewing individual articles.

Translation of Evidence to Guidelines

Format. The guideline document contains 14 guidelines. The format for each guideline is outlined in Table 40 of the original guideline document. Each guideline contains one or more specific "guideline statements," which are presented as "bullets" that represent recommendations to the target audience. Each guideline contains background information, which is generally sufficient to interpret the guideline. A discussion of the broad concepts that frame the guidelines is provided in the preceding section of this report. The rationale for each guideline contains a discussion of specific topics that support the guideline statements, together with a classification of the strength of evidence. The guideline concludes with a discussion of limitations of the evidence review and a brief discussion of implementation issues and research recommendations regarding the topic.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grade A: It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves health outcomes.

Grade B: It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderately strong evidence that the practice improves health outcomes.

Grade C: It is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence or on the opinions of the Work Group and reviewers, that the practice might improve health outcomes.

Note: Health outcomes are health-related events, conditions, or symptoms that can be perceived by individuals to have an important effect on their lives. Improving health outcomes implies that benefits outweigh any adverse effects.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The grade of recommendation (A, B, or C) and level of evidence (strong, moderately strong, or weak) are defined at the end of the "Major Recommendations" field.

Section 1: Guidelines on Evaluation and Management of Cardiovascular Diseases

Guideline 1: **Evaluation of Cardiovascular Disease in Adult and Pediatric Patients**

Cardiovascular disease (CVD) is prevalent in patients receiving dialysis therapies, and it affects long-term outcomes as well as the ability to deliver dialysis in some situations. Thus, it is important to evaluate the extent of all aspects of CVD in dialysis patients. In those patients with limited life expectancy due to severe non-cardiac comorbidity, evaluation and therapy should be individualized.

1.1. At the initiation of dialysis, all patients--regardless of symptoms--require assessment for CVD (coronary artery disease [CAD], cardiomyopathy, valvular heart disease, cerebrovascular disease [CBVD], and peripheral vascular disease [PVD]), as well as screening for both traditional and nontraditional cardiovascular risk factors. (**C**)

1.1.a. Echocardiograms should be performed in all patients at the initiation of dialysis, once patients have achieved dry weight (ideally within 1 to 3 months of dialysis initiation) (**A**), and at 3-yearly intervals thereafter. (**B**) (see Guideline 6)

1.2. Children commencing dialysis should be evaluated for the presence of cardiac disease (cardiomyopathy and valvular disease) using echocardiography once the patient has achieved dry weight (ideally within 3 months of the initiation of dialysis therapy). (**C**) Children commencing dialysis should be screened for traditional cardiovascular risk factors such as dyslipidemia and hypertension. (**C**)

Guideline 2: CAD

Ischemic heart disease (IHD) due to atherosclerotic CAD is common in dialysis patients. While its evaluation and treatment are important components of the ongoing care of dialysis patients, there are special considerations for both the evaluation and treatment in dialysis patients due to the issues of preservation of kidney function, vascular access, and bleeding tendencies.

2.1. The evaluation of CAD in dialysis patients depends on individual patient status. (**C**)

2.1.a. If the patient is on the kidney transplant waitlist and is diabetic (and initial evaluation is negative for CAD), then evaluation for CAD every 12 months is recommended.

2.1.b. If the patient is on the transplant waitlist but is not diabetic and is classified as "high risk,"* then evaluation for CAD every 24 months is recommended.

2.1.c. If the patient is on the transplant waitlist and is classified as not high risk,* then evaluation for CAD every 36 months is recommended.

*Note: High-risk (more than 20% per 10 years cardiovascular event rate risk) according to Framingham data includes those with two or more "traditional" risk factors, a known history of coronary disease, left ventricle (LV) ejection fraction (EF) $\leq$40%, or PVD.

2.1.d. If the patient is on the transplant waitlist with known CAD (and not revascularized), evaluation for CAD should be performed every 12 months.

2.1.e. If the patient is on the transplant waitlist and has a history of percutaneous transluminal coronary angioplasty (PTCA) or coronary stent, evaluation for CAD should be performed every 12 months.

2.1.f. If the patient has "complete" coronary revascularization (i.e., all ischemic coronary vascular beds are bypassed), the first re-evaluation for CAD should be performed 3 years after coronary artery bypass (CAB) surgery, then every 12 months thereafter.

2.1.g. If the patient has "incomplete" coronary revascularization after CAB surgery (i.e., not all ischemic coronary beds are revascularized), then evaluation for CAD should be performed annually.

2.1.h. If there is a change in symptoms related to IHD or clinical status (e.g., recurrent hypotension, CHF unresponsive to dry weight changes, or inability to achieve dry weight because of hypotension), evaluation for CAD is recommended.

2.1.i. Dialysis patients with significant reduction in LV systolic function (EF<40%) should be evaluated for CAD.

2.1.j. Evaluation for heart disease should occur at initiation of dialysis and include a baseline electrocardiogram (ECG) and echocardiogram (see Cardiomyopathy guideline for echocardiography after dialysis initiation). Both of these tests provide information pertinent to, but not restricted to, CAD evaluation. Annual ECGs are recommended after dialysis initiation.

2.2. In patients fulfilling 2.1.a--2.1.i above, CAD evaluation should also include exercise or pharmacological stress echocardiographic or nuclear imaging tests. "Automatic" CAD evaluation with stress imaging is currently not recommended for all dialysis patients (i.e., patients not fulfilling 2.1.a--2.1.i). Stress imaging is appropriate (at the discretion of the patient's physician) in selected high-risk dialysis patients for risk stratification even in patients who are not renal transplant candidates. (**C**)

2.3. Patients who are candidates for coronary interventions and have stress tests that are positive for ischemia should be referred for consideration of angiographic assessment. (**C**)

2.4. Special considerations in dialysis patients regarding CAD evaluation include the following: (**C**)

2.4.a. To minimize the risk of potential volume overload from the performance of angiographic studies, iso-osmolar radiocontrast media (e.g., iodixanol) should be used.

2.4.b. Some dialysis patients have residual renal function; there are no data on the value of "nephroprotective" strategies to reduce the potential risk of contrast nephropathy in these patients. The use of *N*-acetylcysteine (and iodixanol) is appropriate in dialysis patients with residual renal function, as both may offer benefit without known harm. Sodium bicarbonate and hydration are not routinely recommended, as intravascular volume expansion may pose risk to dialysis patients with increased cardiac filling pressures.

2.5. In patients undergoing invasive coronary procedures, it is important to avoid internal jugular sites and to preserve brachial and radial arteries for future dialysis catheter and arteriovenous fistula creation, respectively. (**C**)

2.6. Patients undergoing planned invasive procedures for evaluation or treatment of CAD should be assessed for hemorrhagic risk and presence of anemia, as anticoagulants and/or antiplatelet agents may be administered adjunctively for percutaneous coronary intervention. (**C**)

Guideline 3: Acute Coronary Syndromes

The diagnosis of acute coronary syndromes (ACS) in dialysis patients and in the general population is usually based on the triad of symptoms, ECG findings, and cardiac biomarkers. The outcomes of patients on dialysis with ACS are often poor, which may be related to the lack of a consistent and standard approach to the treatment of ACS.

3.1. All dialysis patients presenting with ACS should be treated as in the non-dialysis population, with the exception of specific attention to drugs that have altered clearances in kidney failure (e.g., low molecular weight heparin). These therapies include percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), antiplatelet agents, beta-blockers, thrombolytic therapy, and lipid-lowering agents. (**C**)

3.1.a. Dialysis patients with ST-segment elevation myocardial infarction (MI) should receive acute reperfusion therapy (as do patients in the non-dialysis population). With the potential for increased hemorrhagic risk associated with thrombolytic therapy, emergent PCI is the preferred treatment if it is available. (**C**)

3.2. The timing of dialysis in the first 48 hours after ACS should take into account individual risk factors. (**C**)

Guideline 4: Chronic Coronary Artery Disease

The processes by which atherosclerotic disease may be exacerbated by the uremic milieu, and the outcomes of patients on dialysis with established CAD, are worse than outcomes in the general population.

4.1. The medical management of chronic CAD in dialysis patients should follow that of the general population. In particular, patients should receive acetylsalicylic acid (ASA), beta-blockers, nitroglycerin, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), statins, and/or calcium-channel blockers (CCB) as indicated. Dose adjustments are required for medications that are renally excreted or dialyzed. (**C**)

4.2. Unique aspects of management in the dialysis population include:

4.2.a. Maintenance of hemodynamic dry weight. (**C**)

4.2.b. Maintenance of hemoglobin levels in accordance with Kidney Disease Outcomes Quality Initiative Kidney/Disease Outcomes Quality Initiative (K/DOQI) Guidelines (National Kidney Foundation (NKF)-DOQI, 1997). (**B**)

4.2.c. Modification of dosing regimens so that cardiovascular medications do not adversely impact the delivery of dialysis and ultrafiltration. Nocturnal dosing of medications should be considered (**C**).

4.2.d. Loop diuretics to increase urine output may be helpful for those patients with substantial residual renal function (**C**).

4.3. In patients with obstructive CAD lesions, PCI and CABG are appropriate revascularization techniques. (**C**)

4.3.a. Drug-eluting or conventional stents should be implemented according to local practice. The incidence of restenosis after PCI with drug-eluting stents is reduced in the non-dialysis population. As the

risk of restenosis is higher in dialysis patients, the use of drug-eluting stents is favored.

4.3.b. Patients with three-vessel and/or left main disease should undergo CABG as preferred therapy. (**C**)

Guideline 5: Valvular Heart Disease

The presence of valvular heart disease (VHD) impacts long-term outcomes, as in the general population. In addition, VHD in dialysis patients may impair the ability to adequately deliver dialysis, which, in turn, may limit ultrafiltration and toxin removal, resulting in exacerbation of CVD.

5.1. Evaluation of VHD in dialysis patients:

5.1.a. Patients should be evaluated for the presence of VHD and for follow-up of VHD in the same manner as the general population except for frequency of follow-up for aortic stenosis. (**C**)

5.1.b. Special considerations for echocardiographic evaluation in dialysis patients:

5.1.b.i. Dry weight optimization should be achieved prior to testing, to enhance the interpretation of results. (**B**)

5.1.b.ii. The interpretation of repeat echocardiographic evaluations should be done with consideration of the relationship between the echo exam and either the hemodialysis (HD) treatment or the presence or absence of peritoneal dialysis (PD) fluid in the peritoneal cavity. (**B**)

5.2. Management of VHD in dialysis patients:

5.2.a. Published recommendations for the management of VHD in the general population should be followed. (**C**)

5.2.b. Both mechanical and tissue valves can be used for replacement, with similar outcomes, in dialysis patients. (**B**)

5.2.c. Asymptomatic dialysis patients on the transplant waitlist with moderate or more severe aortic stenosis (aortic valve area $\leq$1.0 cm^2) should have annual Doppler echocardiograms (as aortic stenosis progresses faster in dialysis patients than general population). The same frequency of follow-up is appropriate in other dialysis patients who would be suitable candidates for aortic valve replacement based on overall clinical status. (**C**)

5.2.d. Newly or increasingly symptomatic (e.g., displaying dyspnea, angina, fatigue, and unstable intradialytic hemodynamics) patients with VHD should be (re)-evaluated for VHD severity by echocardiography (and referred to a cardiologist for further evaluation if the patient is deemed suitable for intervention on clinical grounds). (**C**)

5.3. Children with VHD should be evaluated by echocardiography. Management of valvular disease should follow recommendation provided by the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Patients With Valvular Heart Disease VI (Bonow et al., 1998). (**C**)

Guideline 6: Cardiomyopathy (Systolic or Diastolic Dysfunction)

The prevalence of systolic or diastolic dysfunction, or overt left ventricular hypertrophy (LVH), is estimated to be at least 75% at dialysis initiation (see also Guideline 1). *De novo* and recurrent heart failure occurs in a substantial proportion of patients on dialysis, and impacts on morbidity and mortality, as well as the ability to deliver adequate dialysis.

6.1. Evaluation of cardiomyopathy (systolic or diastolic dysfunction) in dialysis patients:

> 6.1.a. Dialysis patients should be evaluated for the presence of cardiomyopathy (systolic or diastolic dysfunction) in the same manner as the general population, using echocardiographic testing. (**C**)
>
> 6.1.b. Patients should be re-evaluated if there is change in clinical status (e.g., symptoms of congestive heart failure (CHF), recurrent hypotension on dialysis, postcardiac events) or considered for kidney transplant. (**C**)
>
> 6.1.c. Echocardiograms should be performed in all patients at the initiation of dialysis, once patients have achieved dry weight (ideally within 1-3 months of dialysis initiation) (**A**), and at 3-yearly intervals thereafter. (**B**)
>
> 6.1.d. As in the general population, dialysis patients identified with significant reduction in LV systolic function (EF <40%) should be evaluated for CAD (if not done previously). This evaluation may include both noninvasive testing (stress imaging) and invasive testing (coronary angiography). In patients at high risk for CAD (e.g., those with diabetic chronic kidney disease [CKD]), coronary angiography may be appropriate, even in patients with negative stress imaging tests, due to lower diagnostic accuracy of noninvasive stress imaging tests in CKD patients. (**C**)

6.2. The treatment of cardiomyopathy in the dialysis population is similar to that in the nondialysis population, with the important exception of potential effects of therapeutic agents (e.g., ACE inhibitors or beta-blockers) on intrahemodialytic hemodynamics. (**C**; **B** for carvedilol)

> 6.2.a. Congestive heart failure unresponsive to changes in target dry weight may also be a complication of unsuspected VHD or IHD; clinical re-evaluation should be considered in these patients. (**C**)

6.2.b. Dosing of therapeutic agents may need to be empirically individualized to hemodialysis schedules (in hypotensive patients). (**C**)

6.2.c. The consistent maintenance of euvolemia is a cornerstone of treatment of CHF in dialysis patients. (**C**)

6.3. Target "hemodynamic dry weight" may need to be adjusted to compensate for hemodynamic effects of therapeutic agents. (**C**)

6.4. Children should be evaluated for the presence of cardiomyopathy (systolic and diastolic dysfunction) using echocardiographic testing. (**C**)

Guideline 7: Dysrhythmia

Patients on maintenance dialysis are at increased risk for dysrhythmias, cardiac arrest, and sudden cardiac death (SCD). The risk of sudden cardiac death or cardiac arrest increases with age and dialysis duration.

7.1. Evaluation of dialysis patients:

7.1.a. All dialysis patients, regardless of age, should undergo a routine 12-lead ECG at the initiation of dialysis. (**C**)

7.1.b. Patients with dysrhythmias should be treated in the same manner as the general population with regard to antiarrhythmic agents (including beta-blockers) and pacing devices (including internal defibrillators). Refer to Table 5 in the original guideline document for dosage adjustments and drugs to be avoided. (**C**)

Guideline 8: External Defibrillation

The capability for effective, rapid defibrillation (with negligible risk of inappropriate treatment) is widely available with the development of automatic external defibrillators (AEDs). Given the high prevalence of dysrhythmias (see Guideline 7), the availability of AEDs in dialysis facilities may impact the outcomes of patients who experience cardiac events during dialysis therapy.

8.1. All dialysis units should have on-site capability for external cardiac defibrillation. Automatic external defibrillators are the simplest, most cost-effective means to achieving this guideline, as they do not require advanced life support training by staff for operation, require minimal maintenance, and are designed for use by nonmedical personnel. (**A**)

8.1.a. Basic life support (CPR) training for dialysis unit staff is recommended as an enhancement to the effectiveness of AEDs, as it includes instruction in use of AEDs, airway and circulatory support during cardiorespiratory arrest, and management of noncardiac emergencies (such as choking). (**B**)

8.1.b. Non-automatic defibrillators are also appropriate devices for providing on-site defibrillator capability, but they require more maintenance and operators certified in advanced cardiac life support (ACLS). (**B**)

8.1.c. All dialysis units caring for pediatric patients need to have on-site external automatic defibrillators and/or appropriate pediatric equipment available. Automated external defibrillators may be used for children 1 to 8 years of age, and should ideally deliver pediatric doses and have an arrhythmia detection algorithm (Cecchin et al., 2001; Atkins, Hartley, & York, 1998; Samson, Berg, & Bingham, 2003). (**C**)

8.1.d. The goal should be the availability of AEDs in all dialysis units within 12 months of the publication of these Guidelines. (**C**)

Guideline 9: Cerebrovascular Disease

Stroke is the third leading cause of death in the general population in the U.S. and many other countries, with large economic and human burdens as a consequence. Patients with CKD are at increased risk for stroke relative to the general population.

9.1. All dialysis patients should follow the AHA Guidelines for the prevention, screening and evaluation, and treatment of stroke. A summary of the AHA guidelines with any caveats related to dialysis patients is shown in the table below. (**C**)

9.2. Special considerations in dialysis patients include:

9.2.a. Anticoagulation in nonvalvular atrial fibrillation: Dialysis patients are at increased risk for bleeding and careful monitoring should accompany intervention. (**C**)

9.2.b. Acute stroke in dialysis patients: Given that acute stroke syndromes can be due to either thrombotic or bleeding events in dialysis patients, the immediate goal of localization and cause is particularly important in dialysis patients because of increased risk of bleeding associated with anticoagulants in this population. Therefore, imaging with established methods should be undertaken. (**C**)

9.3. Treatment of stroke and transient ischemic attack (TIA):

9.3.a. Treatment of TIAs and strokes should follow the same principles used in the general population for both medical management and surgical management, with the exception of thrombolytics in HD patients. (**C**)

9.3.a.i. Assessment of the risk of bleeding in patients recently receiving heparin on dialysis should be conducted when considering the use of thrombolytics. (**B**)

Table: AHA Guidelines for the Prevention, Screening and Evaluation, and Treatment of Stroke, with K/DOQI Modifications

	AHA Guideline	K/DOQI Modification
Prevention		
General	Regular screening for hypertension (HTN) and appropriate management as summarized in the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII). Encourage patients to stop smoking. Provide counseling, nicotine replacement, and formal programs when available. In diabetics, careful control of hypertension is important. Glycemic control is recommended to reduce microvascular complications. ***Diet/Nutrition***: A healthy diet containing at least five servings of fruits and vegetables may decrease the risk of stroke and is therefore encouraged.	Target blood pressure (BP) in dialysis patients is less certain than in the general population. See guideline 10 in this document. In addition, see caveats in Guideline 10 on tobacco use, diet, and diabetes.
Asymptomatic Carotid Stenosis	Endarterectomy may be considered in patients with high-grade asymptomatic carotid stenosis. Careful patient selection guided by comorbid conditions, life expectancy, patient preference, as well as other factors, including gender followed by a thorough discussion of the risks and benefits of the procedure is necessary. Patients should also be thoroughly evaluated for other treatable causes of stroke.	
Atrial Fibrillation	Antithrombotic therapy (warfarin and aspirin) should be considered for patients with nonvalvular atrial fibrillation, based on an assessment of their risk of embolism and risk of bleeding complications.	Dialysis patients are at increased risk for bleeding and careful monitoring should accompany intervention.
Screening/Evaluation		

	AHA Guideline	K/DOQI Modification
Transient Ischemic Attack (TIA)	***Imaging of the brain***: Patients with symptoms suggesting a TIA should receive a computed tomography (CT) scan of the head in the initial diagnostic evaluation to exclude a rare lesion such as a subdural hematoma or brain tumor. A CT scan may also demonstrate an area of brain infarction appropriate to TIA symptoms that may influence subsequent management. Substitution of magnetic resonance imaging (MRI) for CT, for the evaluation of TIA, is not warranted.	
	Imaging of the vessels: Magnetic resonance angiography (MRA) provides sufficient images for evaluation of vertebrobasilar ischemia. Duplex ultrasonography is a screening tool that can be used to determine those with significant stenosis of the carotid arteries. This should be followed by arteriography to determine vessels best suited for intervention.	
Acute Stroke	***Imaging***: The immediate goal in an acute stroke is localizing and exclusion of other causes for symptoms. A CT scan with contrast is recommended as the primary tool for evaluation for an acute stroke. A follow-up CT in 2 to 10 days is recommended for negative CT scans when further documentation is necessary or when the provider suspects that transformation to hemorrhage has occurred. Magnetic resonance imaging is useful for posterior circulation strokes, small hemorrhages, or when dating the hemorrhage is needed, but is not recommended for routine use. Imaging vessels is not necessary in acute stroke. Techniques such as ultrasound	

	AHA Guideline	K/DOQI Modification
	or magnetic resonance angiography may serve as a screening procedure for considering carotid angiography and monitoring of vascular abnormalities.	
	Treatment	
TIA	***Antiplatelet agents***: Daily aspirin should be used for patients who have an atherothrombotic TIA to reduce the risk of recurrent stroke. ***Ticlopidine***: Ticlopidine is limited by its side effects and should be used in patients intolerant to aspirin or who have had a major ischemic event despite aspirin. ***Clopidogrel***: Clopidogrel is limited by its side effects and should be used in patients intolerant to aspirin or who have had a major ischemic event despite aspirin. ***Anticoagulants:*** Warfarin is recommended for subjects with atrial fibrillation who have a TIA. A target international normalized ratio (INR) of 2.5 is recommended. Warfarin is also recommended for patients who are at high risk for other sources of cardioembolism. Aspirin may be used for those that have contraindications to oral anticoagulation.	Dialysis patients are at high risk for bleeding, and adequate precautions should be taken to prevent bleeding associated with antiplatelet agents and anticoagulants.
	Surgical management of carotid disease: Patients with a recent TIA or nondisabling stroke with an ipsilateral carotid stenosis >50% may benefit from surgery. Benefits vary by risk factors and are greatest among men, nondiabetics, and those with hemispheric symptoms and angiographically demonstrated ulcers.	
	Angioplasty and stent	

	AHA Guideline	K/DOQI Modification
	placement: Not currently recommended.	
Stroke	Intra-arterial thrombolysis should be considered investigational. Intravenous tissue plasminogen activator is recommended within 3 hours after the onset of ischemic stroke. This should be done in the setting of a stroke confirmed by CT. It should not be used if the patient has had heparin during the prior 48 hours.	The stipulation of excluding patients who have had heparin during the 48 hours prior to thrombolysis was not designed to address dialysis patients on intermittent dialysis, and would eliminate the majority of dialysis patients on thrombolytics. Therefore, the use of thrombolytics in dialysis patients should be considered on an individual basis.
	Heparin therapy is not recommended as thrombolytic therapy	
	Surgery: Emergent carotid endarterectomy is not recommended.	

Guideline 10: Peripheral Vascular Disease

Both diabetic and nondiabetic dialysis patients are at risk for PVD, with approximately 15% of incident patients having a clinical diagnosis of PVD.

10.1. Diagnosis of PVD:

10.1.a. At the time of dialysis initiation, all patients should be evaluated for the presence of PVD. (**C**)

10.1.b. Evaluation should include physical examination including assessment of arterial pulse and skin integrity. (**C**)

10.1.c. Further specialized studies, such as duplex studies or invasive testing, should be undertaken if abnormalities are detected upon physical examination and interventions are considered. (**C**)

10.2. Approach to therapy of PVD: (**C**)

10.2.a. Patients with PVD should be treated in the same manner as the general population in regard to smoking cessation, lipid-lowering therapy, glycemic control, blood pressure control, and the use of ACE inhibitors and antiplatelet agents. In addition, supervised exercise regimens and medications to increase vasodilation should be considered in patients with claudication and without critical leg ischemia. Established national guidelines, similar to those for stroke, are not available for PVD in the general population.

Section II: Guidelines on Management of Cardiovascular Risk Factors

Guideline 11: Diabetes

11.1. All dialysis patients who have diabetes should follow the American Diabetes Association guidelines ("Standards of Medical Care in Diabetes," 2004; Franz et al., 2003). (**C**).

Guideline 12: Blood Pressure

The management of blood pressure is an important component of CVD risk management for all aspects of CVD: CAD, cardiomyopathy, VHD, CBVD, and PVD. There are unique challenges in both the measurement and management of blood pressure in dialysis patients.

12.1. Measurement of blood pressure:

12.1.a. In patients who have undergone multiple surgical procedures for vascular accesses in both arms, blood pressure should be measured in the thighs or legs. However, health-care professionals should use appropriate cuff size and measure blood pressure only in the supine position. (**B**)

12.2. Predialysis and postdialysis blood pressure goals should be <140/90 mm Hg and<130/80mmHg, respectively. (**C**)

12.3. Management of blood pressure by adjustment of dry weight:

12.3.a. Management of hypertension in dialysis patients requires attention to both management of fluid status and adjustment of antihypertensive medications. This requires close collaboration among health-care providers. (**B**) Excessive fluid accumulation between dialysis sessions should be managed with: (**B**)

Education and regular counseling by dietitians

Low sodium intake (2-3 g/day sodium intake)

Increased ultrafiltration

Longer dialysis

More than 3 dialysis treatments per week

Drugs that reduce salt appetite

12.4. Management of hypertension with drugs in dialysis patients:

12.4.a. Drugs that inhibit the renin-angiotensin system, such as ACE inhibitors or angiotensin II-receptor blockers should be preferred because they cause greater regression of left ventricular hypertrophy (LVH), reduce sympathetic nerve activity, reduce pulse wave velocity,

may improve endothelial function, and may reduce oxidative stress. (**C**)

12.4.b. Antihypertensive drugs should be given preferentially at night, because it may reduce the nocturnal surge of blood pressure and minimize intradialytic hypotension, which may occur when drugs are taken the morning before a dialysis session. (**C**)

12.4.c. In patients with difficult-to-control hypertension, the dialyzability of antihypertensive medications should be considered (see Table 10 in the original guideline document). (**C**)

12.5. Determination and management of blood pressure in children should follow recommendations by The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents ("The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents," 2004). (**C**)

12.5.a. Optimal systolic and diastolic blood pressure should be <95% for age, gender and height. (**B**)

12.5.b. Management of hypertension on dialysis requires attention to fluid status and antihypertensive medications, minimizing intradialytic fluid accumulation by (**C**):

Education by dietitians every 3 months

Low salt intake (2 g/day sodium intake)

Increased ultrafiltration

Longer dialysis duration

Intradialytic sodium modeling to minimize intradialytic hypotension

More than 3 dialysis treatments per week

Antihypertensives: consider if medications are cleared on dialysis.

Guideline 13: Dyslipidemia

Since the NKF K/DOQI Clinical Practice Guidelines for Managing Dyslipidemia in Chronic Kidney Disease Patients were established only recently (K/DOQI, 2003), the Work Group refers the reader to those guidelines. However, the Work Group adds the information on four recent studies that provide some new insights on the inverse association between cholesterol level and mortality, as well as further indirect evidence of the beneficial effects of lipid-lowering therapy. Furthermore, unpublished results of the recently completed "4D Trial" on the effect of statins in chronic HD patients recently became available and will be discussed.

Management of dyslipidemias for prepubertal children with CKD and CKD Stage 5 should follow recommendations by National Cholesterol Expert Panel in Children

and Adolescents. Postpubertal children or adolescents with CKD Stages 4 and 5 should follow the recommendations provided in the K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease (K/DOQI, 2003).

Guideline 14: Smoking, Physical Activity, and Psychological Factors

While there are few data specific to CVD in dialysis patients regarding smoking, physical activity, and psychological factors (depression, anxiety, and hostility), the evidence in the general population is clearly in favor of addressing each of these issues. In order to ensure that clinicians caring for dialysis patients do not overlook the importance of each of these factors, the Work Group has dedicated an entire guideline to them.

14.1. All dialysis patients should be counseled and regularly encouraged to stop smoking. (**A**) Referral to smoking cessation specialists is recommended. (**C**)

14.1.a. Special consideration should be given to cessation of smoking in depressed individuals with little ability to engage in physical activity. (**C**)

14.2. All dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity. (**B**)

14.2.a. Unique challenges to exercise in dialysis patients need to be identified in order to refer patients appropriately (e.g., to physical therapy or cardiac rehabilitation) and to enable the patients to follow regimens successfully. Such challenges include orthopedic/musculoskeletal limitations, cardiovascular concerns, and motivational issues. (**C**)

14.3. Measurement of physical functioning:

14.3.a. Evaluation of physical functioning and re-evaluation of the physical activity program should be done at least every 6 months. (**C**)

14.3.b. Physical functioning can be measured using physical performance testing or questionnaires (e.g., SF-36). (**C**)

14.3.c. Potential barriers to participation in physical activity should be assessed in every patient. (**C**)

14.4. Physical activity recommendations:

14.4.a. Many dialysis patients are severely deconditioned and therefore may need a referral for physical therapy to increase strength and endurance to the point where they are able to adopt the recommended levels of physical activity.

14.4.a.i. Patients who qualify for cardiac rehabilitation should be referred to a specialist. (**C**)

14.4.a.ii. The goal for activity should be for cardiovascular exercise at a moderate intensity for 30 minutes most, if not all, days per week. Patients who are not currently physically active should start at very low levels and durations, and gradually progress to this recommended level. (**C**)

- 14.4.b. Follow-up:

14.4.b.i. Physical functioning assessment and encouragement for participation in physical activity should be part of the routine patient care plan. Regular review should include assessment of changes in activity and physical functioning. (**C**)

14.5. Depression, anxiety, and hostility should be identified and treated in dialysis patients. (**B**)

> 14.5.a. Every dialysis patient should be seen by the dialysis social worker at initiation of dialysis, and at least biannually thereafter, to assess the patient's psychological state, with specific focus on the presence of depression, anxiety, and hostility. (**C**)
>
> 14.5.b. Dialysis patients should be treated for depression, anxiety, and hostility if they are experiencing these psychological states. (**C**)

Guideline 15: Anemia

The impact of anemia on CVD (specifically, LVH) and exacerbation of CAD is well described in the dialysis population. Given the prevalence of anemia in the dialysis population, and its association with poor outcomes, anemia is considered a "uremic-specific" CVD risk factor.

15.1. All dialysis patients with anemia should follow the K/DOQI Guidelines for Treatment of Anemia (NKF-DOQI, 1997).

Guideline 16: Arterial Stiffness, Vascular and Valvular Calcification, Calcium, Phosphorus and Parathyroid Hormone

The role of abnormalities of calcium, phosphorus, and parathyroid hormone (PTH) in contributing to arteriosclerosis, subsequent arterial stiffness, calcification, and cardiac valve calcification is an area of intense research. The importance of these parameters to CVD outcomes and the biological plausibility of these variables in CVD processes require attention to them as "uremia-related" risk factors.

16.1. All dialysis patients should have pulse pressure (PP) determined monthly before dialysis.

> 16.1.a. For PP >60 mm Hg and systolic blood pressure >135 mm Hg, it is recommended that PP be reduced by achieving ideal body weight and the use of antihypertensive medication with the target PP being 40 mm Hg. (**B**)

16.2. Identification and treatment of calcification:

16.2.a. If arterial calcification is identified by plain radiography in any of the following sites (abdominal aorta, carotid arteries, ileo-femoral axis or femoropopliteal axis), identification of calcification at another site should be sought. (**C**)

16.2.b. If vascular calcification is present in two or more sites, consideration should be given to prescription of a non-calcium-containing phosphate binder. (**B**)

16.3. All dialysis patients should follow current K/DOQI Guidelines for treatment of calcium, phosphate, and PTH ("K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease," 2003).

16.3.a. Serum phosphorus should be maintained between 3.5 and 5.5 mg/dL (1.13 to 1.78 mmol/L). (**B**)

16.3.b. PTH should be measured every 3 months using an intact PTH assay (first-generation immunoradiometric assay). (**C**)

16.3.b.i. For prevention of CVD, the target PTH value should be between 150 and 300 pg/mL (16.5 to 33.0 pmol/L). (**B**)

16.3.b.ii. Treatment strategies for PTH values <150 pg/mL (16.5 pmol/L) and >300 pg/mL (33.0 pmol/L) should be developed according to the K/DOQI Bone Disease Guidelines ("K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease," 2003). (**B**)

Section III: State of the Science: Novel and Controversial Topics in Cardiovascular Diseases

Please refer to the original guideline document for discussions on intradialytic hypotension, biomarkers, nutritional and metabolic factors, risk stratification, menopause, preventive foot care in diabetes, and aspirin use.

Definitions:

Recommendation Grades

Grade A: It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves health outcomes.

Grade B: It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderately strong evidence that the practice improves health outcomes.

Grade C: It is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence

or on the opinions of the Work Group and reviewers, that the practice might improve health outcomes.

Note: Health outcomes are health-related events, conditions, or symptoms that can be perceived by individuals to have an important effect on their lives. Improving health outcomes implies that benefits outweigh any adverse effects.

Strength of Evidence

Strong: Evidence includes results from well-designed, well-conducted study/studies in the target population that directly assess effects on health outcomes.

Moderately strong: Evidence is sufficient to determine effects on health outcomes in the target population, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; OR evidence is from a population other than the target population, but from well-designed, well-conducted studies; OR evidence is from studies with some problems in design and/or analysis; OR evidence is from well-designed, well-conducted studies on surrogate endpoints for efficacy and/or safety in the target population.

Weak: Evidence is insufficient to assess the effects on net health outcomes because it is from studies with some problems in design and/or analysis on surrogate endpoints for efficacy and/or safety in the target population; OR the evidence is only for surrogate measures in a population other than the target population; OR the evidence is from studies that are poorly designed and/or analyzed.

The strength of evidence for a group of studies was graded using a rating system that takes into account:

1. Methodological quality of the studies
2. Target population (patients on dialysis or other populations)
3. Study outcomes (health outcomes or surrogate measures for those outcomes)

(See table 42 in the original guideline document).

CLINICAL ALGORITHM(S)

A clinical algorithm is provided in the original guideline document for the treatment of hypertension in dialysis patients.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

For each guideline, the recommended action (guideline statement) for the management of cardiovascular disease (CVD) is first described, with the strength of recommendation (A, B, or C, with A being the strongest) provided for each statement. This is followed by the synopsis of a comprehensive review of literature on that particular topic, with the primary focus on the literature that is specific to the dialysis patients. This review provides the rationale for the guideline statement and the strength of recommendation. The strength of evidence (strong, moderately strong, or weak) of the rationale is provided within this section.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate evaluation and management of cardiovascular disease (CVD) in dialysis patients

POTENTIAL HARMS

Risks associated with many of the recommended diagnostic and therapeutic procedures are addressed in the "Major Recommendations" field of this summary and in the original guideline document.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Dofetilide is contraindicated in patients with creatinine clearance of <20 mL/min. Its use should be avoided in dialysis-dependent patients.
- Metformin is contraindicated in dialysis patients because of decreased clearance and the possibility of lactic acidosis.
- Sotalol is contraindicated in dialysis patients because of decreased clearance.
- Table 12 in the original guideline document titled "Antihypertensive drug therapy in dialysis: guidelines for selection" identifies the following relative or absolute contraindications:
    - Direct vasodilators in patients with angina pectoris, post-myocardial infarction (MI), or hypertrophic cardiomyopathy with diastolic dysfunction
    - Alpha-1-blockers in patients with hypertrophic cardiomyopathy with diastolic dysfunction
    - Beta-blockers in patients with bradycardia, heart block, or sick sinus syndrome; peripheral vascular disease; or asthma/chronic obstructive pulmonary disease (COPD)

- Labetalol in patients with bradycardia, heart block, or sick sinus syndrome; or liver disease
- Verapamil or diltiazem in patients with bradycardia, heart block, or sick sinus syndrome; or with cyclosporine-induced hypertension
- Calcium channel blockers (CCBs) in patients with heart failure (decreased left ventricular [LV] ejection fraction)
- Nicardipine in patients with cyclosporine-induced hypertension
- Methyldopa in patients with liver disease
- Angiotensin-converting enzyme (ACE) inhibitors in patients with erythropoietin-induced hypertension

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Use of the Guidelines

These Guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care, and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these Guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

The recommendations for research contained within this document are general and do not imply a specific protocol.

Limitations of Approach

While the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched, and searches were limited to English language publications. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to the domain experts that were missed by the literature search were included in the review.

Exhaustive literature searches were hampered by limitations in available time and resources that were judged appropriate for the task. The sensitive search strategies required to capture every article that may have had data on each of the questions frequently yielded upwards of 10,000 articles. Given the large number of topics, this approach was not feasible. The difficulty of finding all potentially relevant studies was compounded by the fact that in many studies, the information of interest for this report was a secondary finding for the original studies. We used our best judgment in developing

search strategies to balance the yield of potentially useful articles and feasibility.

Guideline 2: Coronary Artery Disease

- Most studies deal with patients who are eligible for kidney transplantation. There are only sparse data on general dialysis patients.
- The specific noninvasive screening method for coronary artery disease (CAD) is dependent on the institution.
- No decision analysis has been done on the trade-off of performing angiography versus further diminution of residual kidney function.

Guideline 3: Acute Coronary Syndromes

- There have been very few dialysis-specific clinical trials.
- It is difficult to assess bleeding diathesis, and therefore risk associated with glycoprotein (GP) IIb/IIIa inhibitors, in individual dialysis patients.

Guideline 4: Chronic Coronary Artery Disease

- All published studies are retrospective analyses. There are no randomized controlled trials comparing percutaneous coronary intervention (PCI) and surgical bypass of coronary arteries in dialysis patients.
- There have also been no studies in the dialysis population on the newest generation of drug-eluting stents (e.g., stents eluting sirolimus or paclitaxel).

Guideline 5: Valvular Heart Disease

- The mortality risk of nonintervention or delayed intervention is not known.

Guideline 6: Cardiomyopathy (Systolic or Diastolic Dysfunction)

- There is only a single, small trial for carvedilol in dialysis patients.
- There are no data on the use of angiotensin-converting enzyme (ACE) inhibitors in dialysis patients with potential hypotension.
- The longitudinal cohort study on echocardiographic changes in chronic hemodialysis (HD) patients by Foley and Parfrey was conducted in patients recruited from 1982 to 1991, mostly before the use of erythropoietin. Despite the newer therapies that became available since then, cardiac events are still the major cause of death and cardiac mortality increases with years on dialysis, according to United States Renal Data System (USRDS) data. Long-term echocardiographic surveillance of dialysis patients in the modern treatment era is lacking. The appropriate time interval for re-evaluation in chronic dialysis patients is therefore uncertain.

Guideline 7: Dysrhythmia

- Although there is an existing and evolving body of evidence about the primary and secondary prevention of cardiac events in the form of arrhythmias in the general population, such evidence is apparently lacking from the growing population of chronic kidney disease (CKD) and dialysis-dependent patients.
- Without definitive evidence from prospective trials in the dialysis population, there may remain an increased concern over the safety and efficacy of interventions.

Guideline 8: External Defibrillation

- Automatic external defibrillators (AEDs) are easy to operate and the operator does not require medical training, but automatic external defibrillators need to be widely available.

Guideline 9: Cerebrovascular Disease

- There are extensive data from the general population regarding risk factors, screening, and treatment of stroke. However, the epidemiology of stroke is different in the dialysis population. In addition, exposures related to dialysis may alter the effectiveness and complications associated with treatment. All recommendations regarding screening and treatment are opinion-based and should be taken with caution.
- There are limited data regarding stroke that are specific to the dialysis population. Data addressing the association between risk factors and stroke are scant. Data supporting screening for stroke are based on limited and weak data, while data addressing treatment do not exist.
- There are no data in the dialysis population regarding medical or surgical management of stroke. However, due to the high risk of bleeding in the chronic kidney disease population, caution should be used when treating with antiplatelet agents.

Guideline 10: Peripheral Vascular Disease

- There are no randomized, controlled trials of any of the interventions for therapy of peripheral vascular disease (PVD) in dialysis patients.
- The above recommendations are based on retrospective, observational studies in dialysis patients. Further large, prospective observational studies and randomized, controlled trials are warranted.

Guideline 11: Diabetes

- Many of the recommendations supported by the American Diabetes Association (ADA) on the care of diabetes are based on large clinical studies that provide strong evidence for the particular recommendation, but those studies do not target dialysis patients.

Guideline 12: Blood Pressure

- One major limitation of these guidelines is the lack of large-scale clinical trials correlating levels of blood pressure with cardiovascular disease (CVD) events. Particularly puzzling is the U-shaped relationship between systolic blood pressure and cardiovascular morbidity and mortality, and the apparent lack of high blood pressure effects on cardiovascular disease events until systolic blood pressure reaches approximately 180 mm Hg. The increased mortality in patients with lower blood pressure could be related to poor ventricular function. The lack of effects of blood pressure on cardiovascular events over a wide range of blood pressure between 100 and 180 mm Hg could be related to variable ventricular function, and to "survival bias," whereby high-risk patients with higher blood pressure may not have survived to be entered into the study.
- Another limitation of these guidelines is related to the great variability of blood pressure with dialysis and the lack of firm criteria on definition of hypertension in this patient population.
- Another major limitation of these guidelines is the lack of controlled studies on the effect of different blood pressure goals and different therapeutic interventions on CVD events. Most of the recommendations are based on inference from studies performed in the general population with normal renal function. Other studies were performed in patients with various degrees of kidney disease, but not on dialysis therapy, and the outcomes were deterioration of renal function but not CVD.

Guideline 14: Smoking, Physical Activity, and Psychological Factors

Smoking

- Cessation of smoking in dialysis patients may be difficult to achieve, as in the general population.
- There are no comprehensive studies of the use of the pharmacotherapies recommended for smoking cessation in dialysis patients.

Physical Activity

- There are no randomized trials in dialysis patients of the effects of exercise on cardiovascular risk profile; however, there are randomized trials in dialysis patients that demonstrate the effects of exercise training on physical functioning. Many patients are severely debilitated and will require lower levels of rehabilitation efforts. These levels may not be sufficient to modify cardiovascular risks; however, they will prove adequate to improve physical functioning.

Psychological Factors

- Research studies have produced conflicting data that may be due to using different definitions of the constructs, examining components within a construct rather than using the entire construct, or using varying methods of measuring psychological constructs. Additional problems in some studies included small sample sizes, large

percentages of a study population lost to follow-up, and not controlling for variables that could affect the outcome.
- This guideline is largely based upon observational studies, meta-analyses, and review articles. No research could be found that evaluated the association between psychological factors and CVD in dialysis patients.

Guideline 15: Anemia

- There is a clear association between poor outcomes and low hemoglobin, but there are little data to suggest that hemoglobin levels >13 g/dL are associated with improved outcomes. The data supporting an association between anemia treatment and improvements in CVD are limited.

Guideline 16: Arterial Stiffness, Vascular and Valvular Calcification, Calcium, Phosphorus and Parathyroid Hormone

Arterial Stiffness

- The data addressing the relationship between increased pulse pressure (PP) and increased mortality rates are robust, while data relating high pulse pressure with medial calcification are less robust. The data supporting the efficacy of interventions to decrease the pulse pressure and to improve clinical outcomes are relatively weak. Earlier interventions that prevent the development of noncompliant blood vessels might be more effective than the treatment of established vascular stiffness in dialysis patients.

Serum Phosphorus

- The evidence linking hyperphosphatemia to an increased risk of all-cause and cardiovascular mortality is based on observational data. The evidence linking hyperphosphatemia with vascular calcification is based on empirical data that are consistent with clinical observations. The randomized clinical trial comparing sevelamer to calcium-containing phosphate binders showed a convincing decrease in the rate of vascular calcification. However, the demonstration of improved clinical outcomes awaits longer-term studies.
- The mechanisms by which vascular calcification leads to specific cardiovascular events are not clear and further studies are required.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation issues related to each of the guidelines are discussed in the original guideline document.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 2005 Apr;45(3 Pt 2):16-153. [736 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

National Kidney Foundation - Disease Specific Society

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National Kidney Foundation (NKF)

GUIDELINE COMMITTEE

NKF-K/DOQI (National Kidney Foundation-Kidney Disease Outcomes Quality Initiative) Cardiovascular Disease in Dialysis Patients Work Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the National Kidney Foundation (NKF) Web site.

Print copies: Available from the National Kidney Foundation (NKF), 30 East 33rd St., New York, NY 10016. These guidelines are also available on CD-ROM from NKF.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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